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Catalytic Asymmetric Synthesis of *anti*-α,β-Diamino Acid Derivatives

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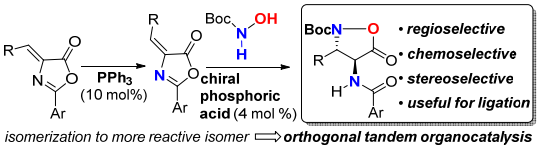
Supporting Information



ABSTRACT: A novel approach to chiral *anti*-α,β-diamino acid derivatives through tandem orthogonal organocatalysis has been developed. Chiral phosphoric acid catalysts control the chemo-, regio-, and stereoselective addition of hydroxylamines to alkylideneoxazolones, while a phosphine catalyst promotes the isomerization of *Z*- alkylideneoxazolones to the more reactive *E*- alkylideneoxazolones.

α,β-Diamino acid derivatives have attracted much attention as important building blocks for the synthesis of various bioactive molecules.[1] In particular, mureidomycins and napsamycins are peptidylnucleoside antibiotics that contain *anti*-α,β-diamino acid residues, and show potent antibacterial activity against strains of *Pseudomonas aeruginosa* (Figure 1).[1,2] One of the most useful strategies for the synthesis of α,β-diamino acid derivatives is an asymmetric Mannich reaction using an α-substituted oxazolone.[1] However, in this type of reaction, the product is limited to α,β-diamino acids with an α-tetrasubstituted carbon stereocenter.[3,4] We planned a novel strategy for a catalytic synthesis of chiral *anti*-α,β-diamino acid derivatives with an α-trisubstituted carbon stereocenter[5] using 4-alkylideneoxazolones **A** and hydroxylamine derivatives as substrates (Scheme 1).

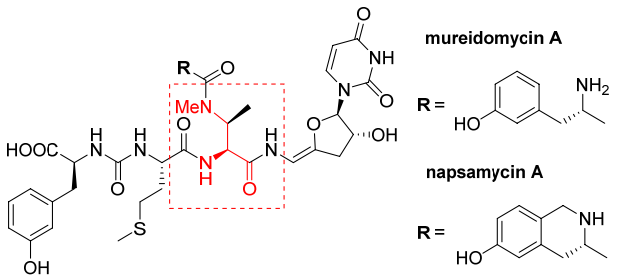
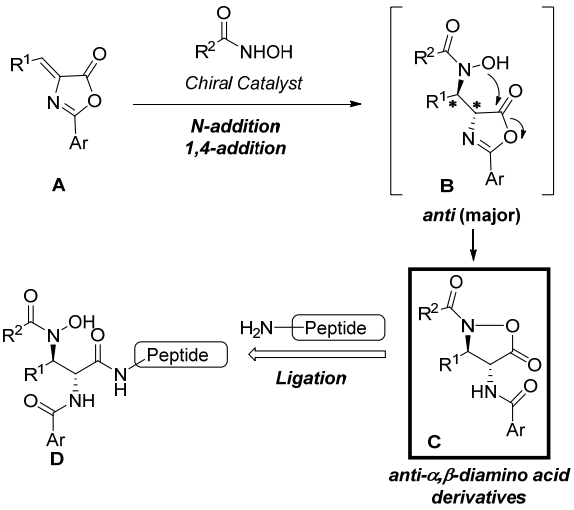


Figure 1. ***anti*-α,β-Diamino acid derivatives**

The salient features of this method are as follows: (i) the stereochemistry of the two vicinal chiral centers would be controlled via aza-Michael adduct **B**, where a subsequent ring-opening reaction[6] of the *anti*-isomer should be favored, affording the *anti*-isoxazolidinone **C**. Epimerization of *syn*-isomer to the more stable *anti*-isomer would also be expected; (ii) intermediate **C** could also be used for peptide ligation to give adduct **D**, whose hydroxylamine moiety could be further elaborated for another peptide ligation;[7] (iii) in the first step, competitive oxa-Michael reaction[8] and 1,2-addition[9] of the hydroxylamine would be fully regulated by a catalyst, resulting in only the desired aza-Michael reaction.

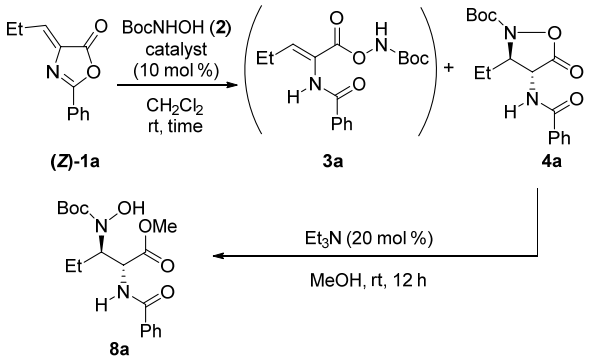
Scheme 1. Synthetic strategy



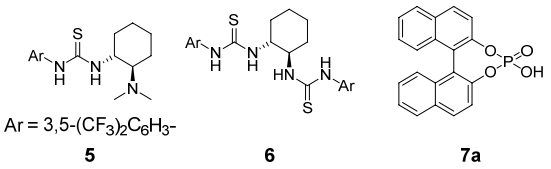
We initially sought efficient catalysts that promoted the aza-Michael reaction of alkylideneoxazolone **(*Z*)-1a** with Boc-NHOH (Table 1). No reaction occurred in the absence of a catalyst (entry 1). Unfortunately, thiourea catalyst **5** that our laboratory had previously developed promoted the undesired *O*-1,2-addition reaction (entry 2),[10] presumably owing to activation of the more acidic OH[8] group of **2** with the tertiary amine moiety of the catalyst. We then screened various organocatalysts without tertiary amine moieties, and found that racemic phosphoric acid catalyst **7a** provided the desired product, 5-oxoisoxazolidine (***anti*-4a**) whose structure was determined by X-ray crystallographic analysis.[10] This indicated that the aza-Michael reaction had occurred, followed by ring

opening of oxazolone intermediate **B** (entry 4). Interestingly, other possible products such as the oxa-Michael and 1,2-addition adducts were not observed, and only ***syn*-4a** was detected as a minor component. After several attempts at isolation, product **4a** was shown to be unstable in silica gel, which led to investigations into derivatizing **4a**. Eventually, we successfully obtained stable *anti*-α,β-diamino acid derivative **8a** via a ring-opening reaction of **4** using methanol (entry 5).

Table 1. Screening of the reaction condition



entry	catalyst	time (h)	yield of **4a** (%)[a]	yield of **8a** (%)[a]	ratio (*anti*:*syn*)
1	none	69	N. R.[b]	-	-
2	**5**	2.5	0[c]	-	-
3[d]	**6**	74	N. R.[b]	-	-
4	**7a**	24	72[e]	-	84:16[f]
5	**7a**	24	n.d.[e,g]	92	80:20[h]



[a] Isolated yields. [b] No reaction. [c] 53% of **3a** was obtained. [d] 5 mol % of **6** was used as catalyst. [e] **3a** was not observed. [f] The ratio was determined based on isolated yields of **4a**. [g] Not determined. [h] The ratio was determined based on isolated yields of **8a**.

Encouraged by these results, we next tried an asymmetric reaction using chiral phosphoric acid **7b** (Scheme 2). We were interested in the differing reactivity between the *E*- and *Z*-isomers,[11,12] so **(*Z*)-1a** and **(*E*)-1a**[10] were investigated under the same reaction conditions. In the presence of 4 mol % of **7b**, the reaction of **(*Z*)-1a** proceeded slowly to furnish the desired compound **8a** in 72% yield (*anti* : *syn* = 74 : 26) with 25% ee (major *anti* isomer) after ring opening with methanol. The absolute configuration of both ***anti*-4a** and ***syn*-4a** was determined by derivatization to known compounds.[13] Very interestingly, the reaction of **(*E*)-1a** occurred much faster than **(*Z*)-1a** to give ***ent*-8a** in higher enantioselectivity. To confirm the reaction rate of each of the isomers, time course analysis of product formation by ^{1}H NMR was conducted, indicating that the reactivity of **(*E*)-1** was much higher.[10] More importantly, the isomerization of each isomer occurred under the reaction conditions, leading to an equilibrium mixture (*Z*:*E* ca. 89:11).[10] This made us revise our strategy to achieve high yield and stereoselectivity; (i) *E*-isomers would be a suitable substrate for achieving excellent stereoselectivity, although suppression of the reaction from the *Z*-isomer would be necessary (Table 2); (ii) the more stable *Z*-isomers could be used as substrates if an additional catalyst could enable isomerization to the *E*-isomers during the reaction, maintaining high stereoselectivities (Table 3).

Scheme 2. Aza-Michael/ring-opening of *Z*- and *E*-1a

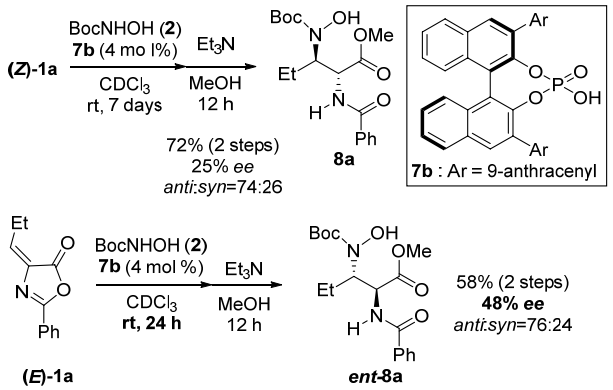
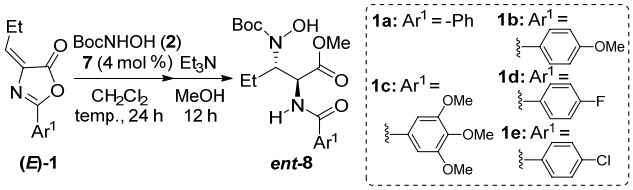
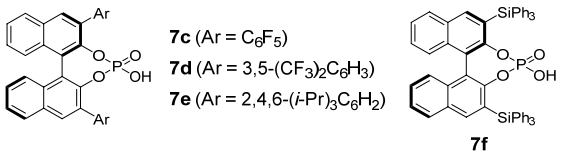


Table 2. Phosphoric acid-catalyzed aza-Michael/ring opening of propylideneoxazolone (*E*)-1



entry	**1**	cat	temp	***ent*-8** (yield, %)[a]	*anti*:*syn*[b] of **8**	ee[c] (%) of **8**
1	**1a**	**7b**	rt	*ent*-**8a** (50)	65:35	58
2	**1a**	**7c**	rt	*ent*-**8a** (70)	65:35	10
3	**1a**	**7d**	rt	*ent*-**8a** (67)	64:36	15
4	**1a**	**7e**	rt	*ent*-**8a** (50)	76:24	68
5	**1a**	**7f**	rt	*ent*-**8a** (53)	75:25	76
6	**1a**	**7f**	0ºC	*ent*-**8a** (56)	76:24	90
7	**1b**	**7f**	0ºC	*ent*-**8b** (48)	81:19	98
8	**1c**	**7f**	0ºC	*ent*-**8c** (59)	71:29	91
9	**1d**	**7f**	0ºC	*ent*-**8d** (44)	75:25	94
10	**1e**	**7f**	0ºC	*ent*-**8e** (46)	70:30	85

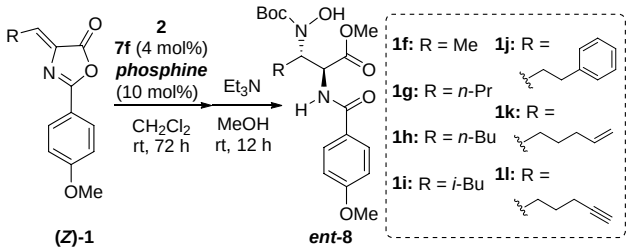


[a] Isolated yields of ***ent*-8** in 2 steps. [b] The ratio was determined by isolated yields. [c] Determined by chiral HPLC analyses.

Thus, we moved on to investigate the reaction of *E*-isomers (Table 2). First, we screened several chiral phosphoric acids **7b–f** at room temperature (entries 1–5), and found that **7f** gave the product in 53% yield with 76% ee (entry 5). Lowering the reaction temperature improved the enantioselectivity to 90% ee, possibly because of suppression of the isomerization of

(*E*)-1 to **(*Z*)-1**, and the direct reaction of **(*Z*)-1** (entry 5 vs 6). We next investigated the effect of the aryl substituent on the oxazolone (entries 7–10).[1] Although the reaction rate was not affected by the presence of either electron-donating or -withdrawing groups, 4-methoxy analog **(*E*)-1b** was found to be an excellent substrate in terms of enantioselectivity (98% ee, entry 7), and the diastereoselectivities were slightly improved as well (*anti*:*syn*=81:19).

Table 3. Phosphoric acid-catalyzed aza-Michael/ring opening of propylideneoxazolone (*Z*)-1 with 2



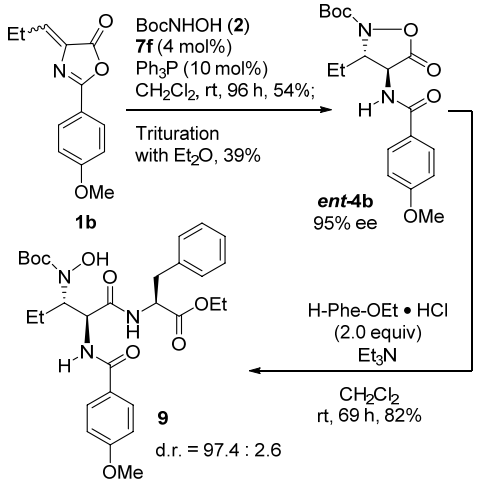
entry	1	phosphine	*ent*-**8** (yield, %)[a]	*anti*:*syn*[b] of **8**	ee[c] (%) of **8**
1[d]	**1b**	Ph_3P	***ent*-8b** (52)	83:17	78
2[d]	**1b**	dppf	***ent*-8b** (38)	72:28	79
3	**1b**	Ph_3P	***ent*-8b** (70)	75:25	71
4	**1f**	Ph_3P	***ent*-8f** (88)	64:36	52
5	**1g**	Ph_3P	***ent*-8g** (60)	75:25	78
6	**1h**	Ph_3P	***ent*-8h** (64)	72:28	84
7[e]	**1i**	Ph_3P	***ent*-8i** (44)	71:29	81
8	**1j**	Ph_3P	***ent*-8j** (60)	73:27	69
9	**1k**	Ph_3P	***ent*-8k** (39)	73:27	80
10	**1l**	Ph_3P	***ent*-8l** (62)	70:30	78

[a] Isolated yields of ***ent*-8** over 2 steps. [b] The ratio was determined by isolated yields. [c] Determined by chiral HPLC analyses. [d] The reaction (first step) was performed at 0 ºC for 120 h. [e] 10 mol % of **7f** was used.

Although high enantioselectivities were achieved using the *E*-isomers as substrates (Table 2), unfortunately these were difficult to prepare.[11] A method using readily available **(*Z*)-1** would therefore be attractive. To solve this problem, we focused on finding a co-catalyst that promoted isomerization of the alkylideneoxazolone (Table 3).[14,15] After testing various organic molecules, iodine was found to promote the reaction. However, ^{1}H NMR experiments showed that iodine itself also catalyzed the racemic aza-Michael/ring opening reaction, which led to only modest enantioselectivities.[10,16] Further investigations into the orthogonal tandem catalysts led to the discovery that phosphines such as $(4\text{-MeOC}_6H_4)_3P$ and $CyPh_2P$ catalyzed not only the isomerization, but also the undesired 1,2-addition reaction. However, Ph_3P only catalyzed the isomerization reaction, and was chosen as the catalyst for the reaction, affording ***ent*-8b** in 52% yield and in 78% ee (entry 1 vs 2).[10] This result strongly suggests that the reaction proceeded mainly through **(*E*)-1b**, which was produced by phosphine-catalyzed isomerization of **(*Z*)-1b**. After optimization of the reaction temperature, this orthogonal tandem reaction was shown to proceed faster at room temperature than at 0 °C without much loss of ee (entry 1 vs 3), probably because the isomerization reaction catalyzed by Ph_3P occurred smoothly at room temperature. The substrate scope of **(*Z*)-1** was then examined under the optimized conditions. Substrates with bulky substitution were likely to provide relatively high enantioselectivity, albeit with slightly decreased yields (entries 3–7). The reactivity of **(*Z*)-1f** itself was high enough to react with **2** without Ph_3P,[10] which decreased the selectivity though the yield of ***ent*-8f** was excellent (entry 4). **(*Z*)-1j–l** with phenyl, alkenyl, and alkynyl groups were also tolerated in this reaction (entries 8–10).

Finally, the coupling reaction of ***ent*-4b** with an α-amino acid was investigated.[17] In this reaction, **1b** was used without separating the *Z*- and *E*-isomers (*Z* : *E* = 81 : 19). As ***ent*-4b** has a tendency to yield racemic crystals, the filtrate obtained by trituration with ether provided ***ent-anti*-4b** with high ee. In this case, 95% ee of ***ent*-4b** was obtained, and was used for the coupling reaction. Instead of MeOH, 2 equivalents of phenylalanine ethyl ester hydrochloride were used in the ring-opening reaction, and gave the desired product **9** in 82% yield (d.r. = 97.4 : 2.6) without any epimerization, indicating that **4** can be used as a substrate for peptide ligations.

Scheme 3. Coupling Reaction



In conclusion, we have developed a novel method for the asymmetric synthesis of *anti*-α,β-diamino acid derivatives with an α-trisubstituted carbon stereocenter using alkylideneoxazolones **1** and a hydroxylamine as substrates, through chiral phosphoric acid-catalyzed[18] tandem aza-Michael/ring opening reaction. We investigated the difference in the reactivity of both *E*- and *Z*-isomers of **1**. To overcome the low reactivity of **(*Z*)-1**, a phosphine was used to catalyze the isomerization of **(*Z*)-1** to **(*E*)-1**. We believe that the present reaction offers an efficient method for the synthesis of peptide-based bioactive compounds through ligation. This is now under investigation and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The experimental details, compound characterization data for all new compounds, the complete copies of NMR and HPLC charts, and CIF file of ***anti*-4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) CCDC 1442977 (***anti*-4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details of the product characterization data.

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